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Short communication

Tenofovir or zidovudine in second-line antiretroviral therapy after stavudine failure in southern Africa

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Abstract

Background: There is debate over using tenofovir or zidovudine alongside lamivudine in second-line antiretroviral therapy (ART) following stavudine failure. We analyzed outcomes in cohorts from South Africa, Zambia and Zimbabwe

Methods: Patients aged ≥16 years who switched from a first-line regimen including stavudine to a ritonavir-boosted lopinavir-based second-line regimen with lamivudine or emtricitabine and zidovudine or tenofovir in seven ART programs in southern Africa were included. We estimated the causal effect of receiving tenofovir or zidovudine on mortality and virological failure using Cox proportional hazards marginal structural models. Its parameters were estimated using inverse probability of treatment weights. Baseline characteristics were age, sex, calendar year and country. CD4 cell count, creatinine and hemoglobin levels were included as time-dependent confounders.

Results: 1,256 patients on second-line ART, including 958 on tenofovir, were analyzed. Patients on tenofovir were more likely to have switched to second-line ART in recent years, spent more time on first-line ART (33 vs. 24 months) and had lower CD4 cell counts (172 vs. 341 cells/μl) at initiation of second-line ART. The adjusted hazard ratio comparing tenofovir with zidovudine was 1.00 (95% confidence interval 0.59-1.68) for virologic failure and 1.40 (0.57-3.41) for death.

Conclusions: We did not find any difference in treatment outcomes between patients on tenofovir or zidovudine; however, the precision of our estimates was limited. There is an urgent need for randomized trials to inform second-line ART strategies in resource-limited settings.

Running head: TDF versus AZT in second-line ART

Introduction

In the absence of routine drug resistance testing in resource-constrained settings, the World Health Organization (WHO) recommends the use of standardized second-line antiretroviral therapy (ART) regimens consisting of a ritonavir-boosted protease inhibitor plus two nucleoside reverse transcriptase inhibitors (NRTI). The NRTI backbone should include lamivudine (or emtricitabine) and tenofovir if stavudine or zidovudine was used in the first-line regimen. However, the K65R mutation, which is associated with tenofovir resistance, is frequent in subtype C viruses, especially in patients on first-line regimens including stavudine [2,3]. Despite these concerns, only few studies have compared clinical outcomes between different second-line regimens in sub-Saharan Africa.

The treatment strategy that should be adopted in case of stavudine failure is of particular importance as most countries are in the process of phasing this drug out [1]. In the absence of virological monitoring in most of these settings, a significant proportion of individuals will have accumulated drug resistance mutations before being switched to other regimens. A recent report on drug resistance patterns in patients failing first-line ART in six African countries suggested that after stavudine failure, zidovudine may be more efficacious than tenofovir [4]. Conversely, a review of HIV-1 resistance mutations data from 35 studies found that tenofovir was more likely than zidovudine to retain antiviral activity following first-line stavudine therapy [5].

We compared clinical outcomes in patients receiving second-line ART including tenofovir or zidovudine after stavudine-failure in a large cohort collaboration in Southern Africa.

Methods

IeDEA-SA

The International epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) is a collaboration of ART programs in seven countries in Southern Africa [6]. Data are collected at ART

initiation and each follow-up visit, using standardized instruments, and transferred to data centers at the Universities of Cape Town, Republic of South Africa (RSA), and Bern, Switzerland. All sites have ethical approval to collect data and to participate in IeDEA-SA.

Patients and outcomes

All patients >16 years who switched from a first-line regimen including lamivudine, stavudine and either nevirapine or efavirenz to a ritonavir-boosted lopinavir-based second-line regimen with lamivudine or emtricitabine and zidovudine or tenofovir were included. Only cohorts with at least 20 patients meeting the eligibility criteria at the time of the database closure in June 2012 were included. Five programs in South Africa, one in Zambia and one in Zimbabwe met inclusion criteria. The sites in South Africa monitored viral load once or twice a year, whereas the cohorts in Zambia and Zimbabwe mainly relied on immunological and clinical criteria to diagnose treatment failure. The primary outcomes were time to death and, in the South African cohorts, time to virologic rebound or failure. Virologic rebound was defined as a single viral load >1,000 copies/ml, at least six months after the initiation of second-line ART. Virologic failure was defined as a viral load >1,000 copies/ml after six months confirmed by a second measurement of >1,000 copies/ml within one year. Loss to follow-up (LTFU) was defined as not returning to the health-care facility for at least six months.

Statistical analyses

We used standard crude and adjusted Cox proportional hazards models, adjusting for age, sex, CD4 cell count, hemoglobin and creatinine at start of second-line ART, year of starting second-line ART and country (RSA versus other). Patients were followed-up from the time of initiation of second-line ART to the date the outcome of interest occurred or, if no outcome observed, to the last follow-up visit. We used marginal structural models to adjust for time-dependent confounding by CD4 count, creatinine and hemoglobin level [7,8]. A directed acyclic graph (DAG) illustrating the causal structure of the covariates used in the marginal structural models is shown in Supplementary Figure S1. The parameters of these models were estimated using inverse probability of treatment weights [9]. For each semester we used multiple imputation to deal with missing values in CD4 count, creatinine and hemoglobin level. Ten imputed datasets were generated and combined using Rubin's rules [10]. Finally, we examined the crude mean CD4 cell count increase during the first year of second-line ART. All analyses were performed using R-2.14.2 (R Project, Vienna, Austria) and Stata version 12.1 (Stata Corporation, College Station, Texas, USA).

Results

Baseline characteristics

Data from 1,256 patients experiencing failure of stavudine-containing first-line ART and switching to second-line ART (tenofovir: 958; zidovudine: 298) were analyzed. Patients receiving tenofovir were older

(median age: 38 vs. 34 years, p<0.001) and less likely to be female (64% vs. 83%, p<0.001) than those given zidovudine. They were more likely to have switched to second-line ART in recent years, spent more time on first-line ART (median: 33 vs. 24 months, p<0.001) and had lower CD4 cell counts at initiation of second-line ART (median: 172 vs. 341 cells/μl, p<0.001) compared to patients on zidovudine. Program- and patient-level characteristics are described in Table 1 and Supplementary Table S1.

Mortality and treatment failure

Data up to four years after start of second-line ART were included with a median follow time of 1.23 years in the tenofovir and 1.87 years in the zidovudine group. In all sites combined, 47 patients died and 287 patients were lost over 2,051 person-years of follow-upl. Patients enrolled in South African cohorts had a median of 1.59 viral load measurements per year spent on second-line. In South Africa, 96 patients developed virologic rebound and 26 developed virologic failure. CD4 cell counts were available in 54% of patients and semesters, values for creatinine in 36% of patients and levels of hemoglobin in 50% of patients. The cumulative percentage of patients who were alive and on ART, who died or were lost over four years after starting second-line ART is shown in Figure 1.

In crude analyses rates of virologic rebound and virologic failure were higher with tenofovir than with zidovudine but HRs were compatible with no difference between the two regimens after adjusting for baseline and time-dependent confounders. The adjusted HR from the marginal structural model was 1.30 (95% CI 0.94-1.80) for virologic rebound and 1.00 (95% CI 0.59-1.68) for virologic failure. Similarly, it was 1.40 (95% CI 0.57-3.41) for mortality (Table 2).

Immunological recovery during second-line ART was inferior in patients on tenofovir compared to those on zidovudine (mean increase: 42 vs. 51 CD4 cells/μl), but the difference in CD4 increase between the two treatment groups was small (difference -9 cells, 95% CI -19 to +1, p= 0.09).

Discussion

This is the largest observational study comparing second-line regimens containing tenofovir or zidovudine in sub-Saharan Africa to date. We compared the hazard of virologic rebound, virologic failure, and death, adjusting for confounding by prognostic factors at baseline and for time-dependent confounding by CD4 count, creatinine and hemoglobin. These risk factors vary with time, predict the choice of second-line ART, and are in turn affected by that choice. We found that there was little evidence of a difference in mortality and virologic rebound or failure between patients on second-line ART containing tenofovir or zidovudine after failing a stavudine containing first-line regimen. Similarly there was little difference in immunological response.

The majority of patients failing first-line ART in sub-Saharan Africa have been previously exposed to stavudine. As this drug is being phased out in most countries, many patients are being switched to another NRTI backbone. Studies estimating the residual activity of tenofovir and zidovudine after

stavudine failure based on drug resistance patterns at first-line failure have been contradictory [4,5]. Most studies that evaluated outcomes of second-line ART including tenofovir have shown good treatment responses [11–14]. These findings could, however, be driven by the response to the potent ritonavir-boosted protease inhibitor during the first year of second-line ART. Indeed, the two studies showing high rates of re-suppression after first-line failure with proven drug resistances only reported on 12-month outcomes [12,14]. Our study extends these results by showing that outcomes in patients on tenofovir-containing second-line ART are favorable and similar to those observed with zidovudine for up to four years after initiating second-line ART.

The number of outcomes observed in our study was relatively small and statistical power to detect smaller differences between the two regimens was therefore limited. Also, there were important imbalances in baseline characteristics. For instance, patients on tenofovir spent more time on their first-line regimen: they may have developed drug resistance mutations limiting the effectiveness of second-line ART. Patients given tenofovir also had lower CD4 cell counts at initiation of second-line ART than those given zidovudine. Finally, missing values were a problem. We imputed these data and adjusted for baseline and time-dependent confounding; however, we recognize that residual confounding may have affected our results. As we had little data on drug resistance patterns, we were unable to assess the impact of specific resistance mutations on treatment outcomes. However, drug resistance is only one of multiple important drivers of treatment failure. Incomplete adherence may be an even stronger risk factor for treatment failure in patients on second-line ART.

In conclusion, we did not detect important differences in virologic or immunologic response or mortality in patients who failed a stavudine containing first-line regimen and switched to second-line ART including tenofovir or zidovudine. The precision of our estimates was, however, limited and there is clearly a need for continued monitoring of outcomes of second-line ART in sub-Saharan Africa, within IeDEA and other cohort collaborations. Although our results are reassuring, randomized trials would provide stronger evidence regarding optimal choices of second-line ART in Southern Africa.

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Potential conflicts of interests

We declare no competing interests.

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Table 1: Comparison of patients at the initiation of second-line ART, by treatment regimen.

	Second-line ART		p-value	Total
	TDF/3TC/LPVr	AZT/3TC/LPVr		
	(N=958)	(N=298)		(N=1,256)
Female (%)	613 (64.0)	246 (82.6)	<0.001	859 (68.4)
Median age, years (IQR)	38 (33-45)	34 (30-39)	<0.001	37 (32-44)
Median CD4 count, cells/μl (IQR)	172 (93-278)	341 (197-501)	<0.001	207 (104-343)
missing (%)	423 (44.2)	100 (33.6)		523 (41.6)
Median months on first-line ART (IQR)	33 (22-45)	24 (13-37)	<0.001	31 (19-44)
Median hemoglobin, g/dl (IQR)	12.4 (11.0-13.7)	12.2 (11.2-13.3)	0.53	12.4 (11.0-13.6)
missing (%)	456 (47.6)	95 (31.9)		551 (43.9)
Median creatinine, ml/min (IQR)	74 (62-90)	64 (53-78)	0.003	73 (61-88)
missing (%)	538 (56.2)	239 (80.2)		777 (61.9)
Calendar year of ART start (%)			<0.001	
<2007	16 (1.7)	84 (18.1)		70 (5.6)
2007	104 (10.9)	69 (23.2)		173 (13.8)
2008	228 (20.8)	65 (21.8)		293 (23.3)
2009	303 (31.6)	68 (22.8)		371 (29.5)
2010	237 (24.7)	39 (13.1)		276 (22.0)
2011	70 (7.3)	3 (1.0)		73 (5.8)
Country (%)			<0.001	
South Africa	235 (24.5)	209 (70.4)		445 (35.4)
Zambia	674 (70.4)	84 (27.9)		757 (60.3)
Zimbabwe	49 (5.1)	5 (1.7)		54 (4.3)

ART, antiretroviral treatment; TDF, tenofovir; 3TC: lamivudine, LPVr: lopinavir-ritonavir, AZT: zidovudine, IQR, interquartile range,

Table 2: Mortality, virologic rebound and virologic failure in patients on tenofovir or zidovudine containing second-line regimen after failing a stavudine containing first-line regimen in Southern Africa.

|	No. of events (%)		Incidence rate (per 100 py)		Unadjusted hazard ratio from Cox model (95% CI)	Adjusted hazard ratio from standard Cox model (95% CI)	Adjusted hazard ratio from marginal structural model (95% CI)
	TDF	AZT	TDF	AZT			
Virologic rebound	55 (23.40)	41 (19.50)	23.60	8.28	1.96 (1.53-2.50)	1.30 (0.94-1.79)	1.30 (0.94-1.80)
Virologic failure	11 (4.68)	15 (7.14)	4.73	3.03	2.21 (1.53-3.21)	1.04 (0.63-1.73)	1.00 (0.59-1.68)
Mortality	36 (3.76)	11 (3.69)	2.60	1.65	1.70 (0.83-3.51)	1.39 (0.57-3.39)	1.40 (0.57-3.41)

* Adjusted for age, sex, CD4 cell count, hemoglobin and creatinine at baseline, year of starting second-line ART and country.

TDF: tenofovir, AZT: zidovudine, 95% CI: 95% Confidence Interval, py: person years
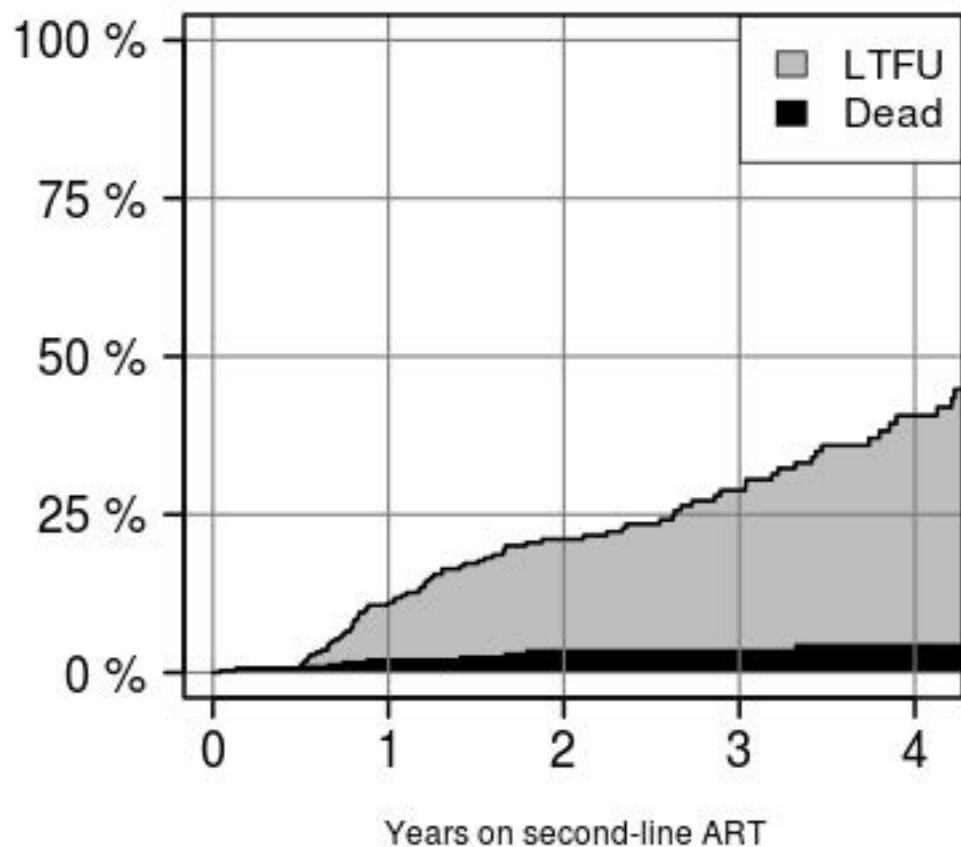
Virological rebound: viral load >1,000 copies/ml after at least 6 months of follow-up

Virological failure: 2 consecutive viral loads>1,000 copies/ml after at least 6 months of follow-up

A: Cumulative incidence in TDF group
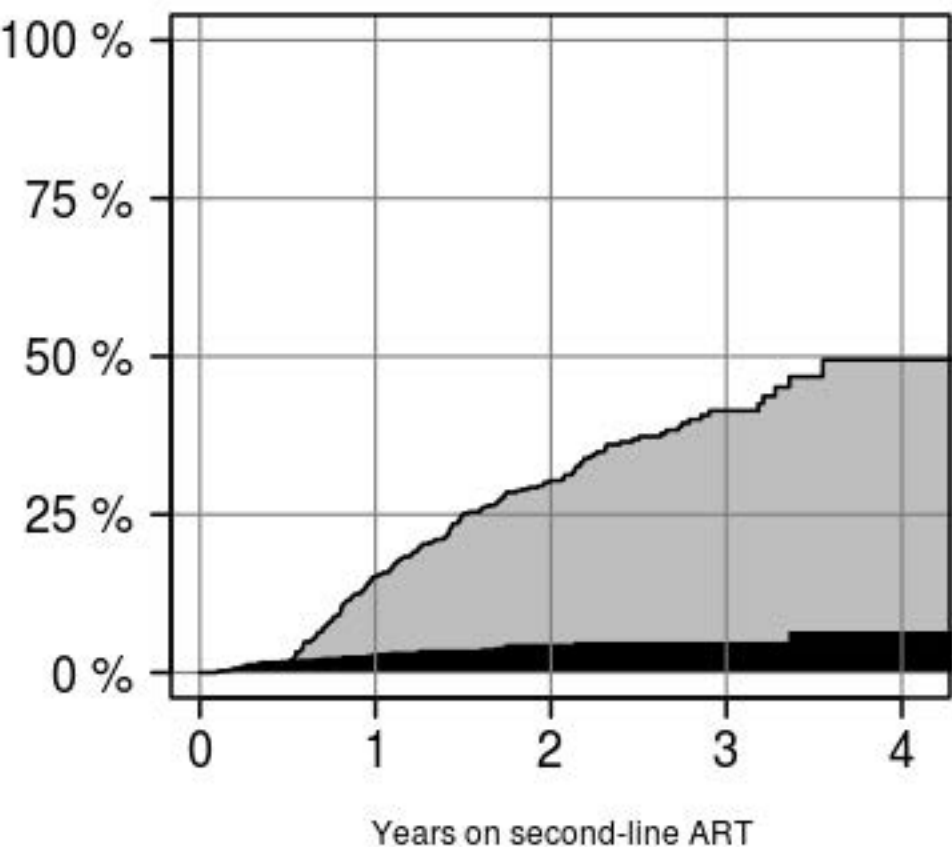
B: Cumulative incidence in AZT group

LTFU

Dead

Years on second-line ART
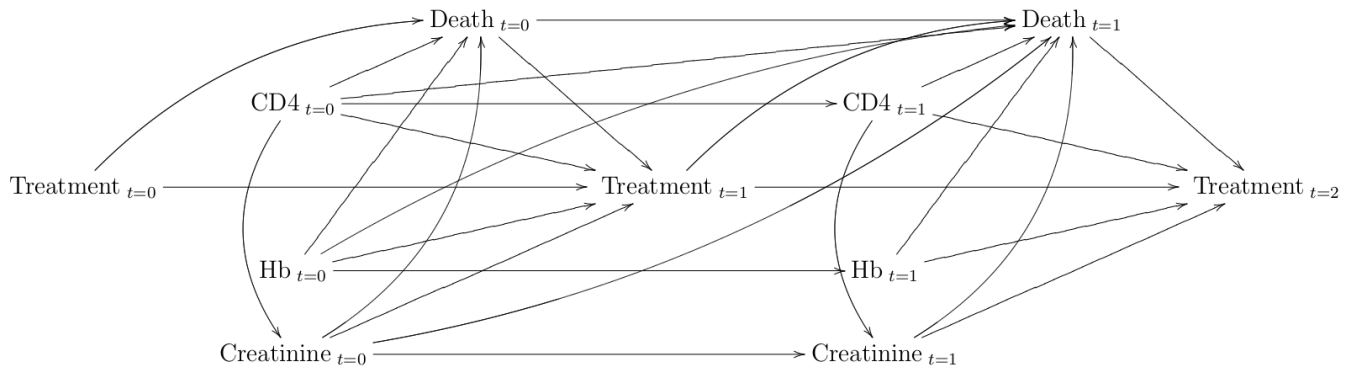
Years on second-line ART

Supplementary Table S1: Characteristics of patients included in an analysis comparing zidovudine with tenofovir containing second-line antiretroviral therapy in Southern Africa.

Sites	No. of patients	Second-line ART		Female (%)	Median age in years (IQR)	Median follow-up time (days)	Median number of VL per year on SL (IQR)
		TDF/3TC/LPVr	AZT/3TC/LPVr				
South Africa							
Aurum CS	33	21 (63.6)	12 (36.4)	20 (60.6)	39 (33-44)	405 (267-741)	2.29 (2.03-2.75)
Gugulethu	88	34 (38.6)	54 (61.4)	70 (79.6)	34 (31-38)	622 (435-1,592)	2.86 (2.41-3.18)
Khayelitsha	186	146 (78.5)	40 (21.5)	129 (69.4)	35 (31-39)	355 (197-491)	0 (0-0)
Themba Lethu	115	24 (20.9)	91 (79.1)	100 (87.0)	35 (30-38)	569 (317-920)	2.31 (1.67-3.17)
Tygerberg	23	10 (43.5)	13 (56.5)	19 (82.6)	33 (27-39)	246 (80-379)	1.32 (0-4.11)
Zambia							
MOH-CIDRZ	757	674 (89.0)	83 (11.0)	479 (63.3)	39 (33-45)	531 (304-802)	NA
Zimbabwe							
Newlands	54	49 (90.7)	5 (9.3)	42 (77.8)	40 (33-45)	735 (357-1,226)	NA
Total	1,256	958 (76.3)	298 (23.7)	43,654 (60.1)	37 (32-44)	489 (292-826)	1.59 (0-2.78)

TDF: tenofovir, 3TC: lamivudine, LPVr: lopinavir-ritonavir, AZT: zidovudine, CS: community site, CIDRZ: Centre for Infectious Disease Research in Zambia, IQR: inter-quartile range; VL: viral load; SL: second-line antiretroviral therapy; NA: not applicable

Supplementary Figure S1: Directed acyclic graph (DAG) illustrating the causal structure of the covariates used in the marginal structural model of the effect of zidovudine vs. tenofovir in second-line ART on mortality.

* Hb: hemoglobin